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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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CASWELL FILE

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

August 8, 1983

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SUBJECT: Metalaxyl; Rat and Mouse Chronic Feeding Studies; Further Assessment of Oncogenic Potential Including Statistical Analysis and Risk Assessment
CASWELL#375AA

The attached Evaluation of Metalaxyl Potential for Carcinogenicity demonstrated by C-cell Adenomas in the two year rat study indicates that Metalaxyl should be considered to be an oncogen.

It is appropriate to perform quantitative risk assessment of potential risks to man associated with various exposures. At this time exposure data for applicators are not available but the current TMRC estimated daily life exposure is .0049 mg/kg body weight/day. The most conservative estimate of the upper 95% confidence bound on the lifetime risk associated with this level of daily exposure is .0765 per person i.e., 76.5 per thousand.

It is recommended that a complete work-up of exposure be performed so that risks can be computed for various types of applicators. It also seems appropriate to consider whether there are benefits which offset this level of risk.

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Chronic 2-Year Metalaxyl Feeding Study in Rats

The two year study of CGA-48988 in Dietary Administration to Sprague-Dawley Rats was conducted at Life Science Research, between September 28, 1977 and October 6, 1979. The final report is dated September 23, 1980. This study differed from current U.S. chronic studies in rats in that:

1) Five rats were allocated to each cage so as to balance the total body weights of the group in each cage;

2) Cages were randomized to treatment so that the cage is the primary study unit not the rat;

3) The placement of the cages remained fixed throughout the study except that the female cages were moved in sequence to take up the spaces vacated by the 8 cages of males that were sacrificed at 56 weeks rather than at 52 weeks.

4) Blood samples were drawn from 1 set of animals during the first year and a second set of animals during the second year. Thus effects due to variability within and among animals differs in year 1 and year 2 analyses of liver function and haematology markers.

The original and the April 21, 1983 submission do not consider any of these design features in their analyses and text.

There were 80 animals per group fed CGA-48988 at nominal concentration of 0, 50, 250 and 1250 ppm at the beginning of study. The last 2 cages per sex per group were used as the source of blood samples during the first year of study. This same subset of cages (of rats) were the animals killed during weeks 55/56. No pathology effect was evident among animals dying during the first 55 weeks or at the interim sacrifice. However, serum protein, liver function tests and white cell counts did show effects at low and mid-dose levels. They appeared during the first 12 weeks of study and tended to disappear by week 78. Data on food intake and food efficiency are remarkedly similar across treatment groups. Patterns of abnormal blood chemistry and liver function differ over time and survivors show fewer functional effects. However liver weights and relative liver weights indicate significant elevation for the higher dosed males and particularly the 1250 ppm females, compared with controls. There is a suggestion of compound related reduction in survival. The April 21, 1983 submission indicates that the

Wilcoxon-Breslow statistic is 3.907 for females with 3 degrees of freedom and an associated P = 0.2718 for the two-tail criterion; however safety testing utilizes the one-tail criterion and this may be reasonably approximated by 1/2 P = 0.136 for females. A larger study could find that the differences between dose groups are statistically significantly different. When the life tables are used one finds that at 15 months there were 68 control 65 (50 ppm) 63 (250 ppm) and 63 (1250 ppm) females remaining in the study. Turning to table 2 of the April 21, 1983 report one find a dose and time related effect for parafollicular adenomas in female rats such that 2 of 68 control, 7 at 50 ppm, 10 at 250 ppm and 5 at 1250 ppm were observed. Moreover no tumors were diagnosed in control or 1250 ppm groups prior to terminal kill, while 3 of the 50 ppm group were detected at 95, 98, 103 weeks, and 5 of the 250 ppm females were diagnosed at deaths occurring at 78-94 weeks. The registrant finds a statistically significant effect at the mid-dose even using the two-tail criterion (rather than the one-tail test used by regulatory agencies in evaluating safety data.) The company does not find a dose-response because of the reduction in effect reported at the high dose. When the high dose is deleted a significant dose-response at $P < .01$ is found for this tumor type in female rats. The rational for deleting the high dose group is illustrated in figure 1 where we observe that all dose groups have a higher response rate than do controls and as this relative risk is at least 2 1/2 we may expect that with a larger study, even the high dose group would be statistically significant, however, the slope of the curve flattens out as the dose increases, suggesting that at low doses the curve of the additional risk over baseline may be supra-linear.

The company has suggested that historical data support the hypothesis that the observed data are homogeneous and that chi-square tests in which control data from 15 studies are substituted for the study control also demonstrate homogeneity based on $P > .05$. Once again the P values offered are two-tailed results. If we estimate the one-tail result as 1/2 the two-tail estimate (see pages 20-22 of J.L. Fleiss, Statistical Methods for Rates and Proportions, Wiley 1973) we find that the P values in Table 8 of the April 21, 1983 are transformed so that the observed study show P = .048, 4 of the historical controls yield P = .009-.036; 6 provide borderline estimates of P = .0565-.1335 and 2 more are suggestive at P = .185 at .201 respectively; only 3 provide reasonable support for the company hypothesis of no effect. Accordingly, we reject the null hypothesis and accept the alternative of a positive dose-response associated with feeding of Metalaxyl to rats.

From the preceeding analysis one would expect that the tolerance extrapolation models such as the Probit or Weibull would be more appropriate than would models based on mechanistic theories of cancer (such as the one-hit, multi-stage and mult-hit models.) All of these models are equally accurate in predicting expected values for the observed data in the observable range. When we use the additive assumption for computing Probit and Weibull estimates of lower 95% confidence bounds associated with attributable levels of risk we find:

	Probit Model		Weibull Model	
Attributable Level of Risk	Associated Lower 95% Bound	MLE Point Estimated	Associated Lower 95% Bound	MLE Point Estimate
1×10^{-1}	0.27	0.80	0.28	0.81
1×10^{-2}	7.6×10^{-4}	6.9×10^{-3}	4.4×10^{-4}	4.6×10^{-3}
1×10^{-3}	5.0×10^{-5}	5.0×10^{-4}	2.5×10^{-5}	3.0×10^{-4}
1×10^{-4}	2.9×10^{-6}	4.9×10^{-5}	2.4×10^{-6}	2.9×10^{-5}
1×10^{-5}	2.9×10^{-7}	4.9×10^{-6}	2.4×10^{-7}	2.8×10^{-6}
1×10^{-6}	2.9×10^{-8}	4.9×10^{-7}	2.4×10^{-8}	2.8×10^{-7}
1×10^{-7}	2.9×10^{-9}	4.9×10^{-8}	2.4×10^{-9}	2.8×10^{-8}
1×10^{-8}	2.9×10^{-10}	4.9×10^{-9}	2.4×10^{-10}	2.8×10^{-9}

The Upper 95% Confidence Bound on the lifetime estimate of cancer risk based on the TMRC Exposure of .0049 mg/kg body weight/day is .0765 based on the additive Weibull Assumption or .047 per person, based on the Additive Probit tolerance assumption.

NOTE : In the preceeding quantative risk assessments the doses used are 0, .38 and 1.928 mg/kg body weight/day. These numbers are obtained by time weighting the achieved doses (shown in Table 6, page 45 of the original September 1980 report off this rat study) and using the surface area adjustment $(60{,}000/4\text{-}500)^{1/3} = 5$ to obtain human equivalent doses in mg/kg of body weight/day.

Chronic 2-Year Feeding Study of Metalaxyl in Mice

This study is less than satisfactory for extrapolation purposes because of the high mortality rates, especially in controls compounded by the presence of Tyzzer's disease. There are however a significant increase in tumor bearing animals with proliferative liver lesions of Type A and/or Type B (as defined by the Company Submission) this issue may be considered as supportive evidence of the liver data observed in the rat study.

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